

Remarks

Claims 1-17, 19-22 and 27-147 are pending in the present application. Claims 35-41, 43-111, 122-129 and 139-147 are withdrawn from consideration. Therefore, claims 1-17, 19-22, 27-34, 42, 112-121 and 130-138 are currently pending and under examination. Claims 5-16 and 117-119 are canceled herein. Claims 1-4, 17, 34, 42, 114-116 and 130-136 are amended herein for clarity and to more particularly define the claimed invention. Claims 148-150 are newly added. Support for the amendments to claims 1-4, 17, 34, 42, 114-116 and 130-136 can be found in the claims as filed, in the paragraph bridging pages 17-18 and in the first full paragraph of page 18 where Applicants describe the membrane form of an antibody and the secretory form of an antibody, in the last paragraph on page 70 where it is stated that “[t]he membrane form of antibody binds these two receptors through the membrane spanning domain that is on the C-terminus of the full-length heavy chain (mHC) as shown in Figure 1.”, throughout the Examples (for example, on page 73, lines 3-16 and Figure 8) where Applicants have described and shown the increased surface presentation of the endogenous membrane form of a monoclonal antibody on the surface of hybridoma cells and elsewhere throughout the specification. Additional support for the amendments to claims 1-4, 17, 34 and newly added claims 148-150 can be found in the claims as filed, on page 40, lines 5-9 where fold increases in the amount of antibody presented on the cell surface of hybridoma cells are described and on page 25, lines 12-16 where various methods of measuring the amount of antibody on the cell surface of hybridomas are described, and elsewhere throughout the specification.

Further support for the amendments to claim 42 can be found in claims 17, 35 and 42 as filed as well as throughout the specification. Further support for the amendments to claims 114 and 131 can be found in the claims as filed and throughout the specification where it is clear that the hybridoma cells of the present invention express monoclonal antibodies that are bound to the cell surface. No new matter is believed to be added by these amendments. In light of the following remarks, applicants respectfully request reconsideration of this application, entry of the new claims and allowance of the pending claims to issue.

Objections to Sequence Listing

The Office Action states that sequences disclosed at least in Figures 2-4 are not accompanied by SEQ ID Numbers. Also stated in the Office Action is that for sequences disclosed as part of the Drawings, the SEQ ID Numbers must be provided as part of the Brief Description of the Drawings.

Enclosed herewith is a diskette containing a substitute Sequence Listing for this application in computer readable form (CRF) and a paper copy of the substitute Sequence Listing in compliance with 37 C.F.R. § 1.821-1.825. This substitute Sequence Listing now includes the primer sequences listed in Figure 2. Applicants hereby certify that the information in the computer readable form on the diskette and in the hard copy of the Sequence Listing is the same and includes no new matter. The enclosed computer readable copy and paper copy of the Sequence Listing are believed to bring the Sequence Listing into full compliance with the sequence rules.

In addition to providing a substitute Sequence Listing, the Brief Description of the Drawings is amended herein to properly reference all of the sequences in Figures 2-4 with a SEQ ID Number. Thus applicants believe this objection has been overcome and respectfully request its withdrawal.

Objections to the Specification

A. According to the Office Action, the use of trademarks has been noted in the application (e.g. Zeocin). Therefore, each letter of the trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

In response, the specification is amended herein to properly reference all trademarks utilized in the application. Therefore, Applicants believe this objection has been overcome and respectfully request its withdrawal.

B. The Office Action states that the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, e.g. on page 83. Thus, the Office Action requests that Applicants delete the embedded hyperlink.

In response, the specification is amended herein to delete this hyperlink. Therefore, Applicants believe this objection has been overcome and respectfully request its withdrawal.

Objection to the Drawings

The Office Action states that the Drawings are objected to because the Brief Description of the Figures refers to panels A, B and C in Figure 13, whereas Figure 13 does not have panels designated A, B or C.

In response, attached hereto is a Replacement Sheet for Figure 13 that properly identifies panels A, B and C. Thus, Applicants believe this objection has been overcome and respectfully request its withdrawal.

Objection to the Claims

According to the Office Action, claim 42 is objected to as being dependent on a non-elected claim and Applicants are required to cancel the claim(s) or amend the claim(s) to place the claim(s) in proper dependent form or rewrite the claim(s) in independent form.

Claim 42 has been rewritten in independent form to recite “[t]he hybridoma cell of claim 17 produced by fusing a myeloma cell comprising a vector, wherein the vector comprises a nucleic acid encoding at least one surface-expressed antibody receptor selected from the group consisting of Igα and Igβ, with a B cell to produce a hybridoma cell comprising at least one surface-expressed antibody receptor selected from the group consisting of Igα and Igβ.” Thus, Applicants believe this objection has been overcome and respectfully request its withdrawal.

Rejections Under 35 U.S.C. § 112, second paragraph

A. The Office Action states that claims 114-121 and 130-138 are rejected under 35 U.S.C. § second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the Office Action, claims 114-121 and 130-138 are allegedly indefinite in the recitation of “a population of hybridoma cells comprising a vector comprising a

nucleic acid encoding Ig $\alpha$  and/or Ig $\beta$  that expresses monoclonal antibody,” because it is allegedly unclear whether it is the population of hybridoma cells, the vector or the nucleic acid that expresses the monoclonal antibody.

In response, claims 114 and 130 are amended herein to recite, in relevant part, “[a] population of hybridoma cells comprising a vector comprising a nucleic acid encoding Ig $\alpha$  and/or Ig $\beta$ , wherein the population of hybridoma cells expresses the endogenous membrane form of a monoclonal antibody bound to the cell surface...” Support for this amendment can be found in the claims as filed as well as throughout the specification where it is clear that the hybridoma cells of the present invention express the endogenous membrane form of a monoclonal antibody bound to the cell surface. Thus, Applicants believe that this rejection, as it applies to claims 114, 130 and their dependent claims (claims 115-116 and 131-138, respectively) has been overcome and respectfully request its withdrawal.

B. According to the Office Action, claims 114-121 and 130-138 are allegedly indefinite in the recitation of “fluorescence intensity of a population of cells,” because it is allegedly unclear whether the measure of intensity refers to a mean, median, modal or some other population-related measure of fluorescence.

As stated above claims 117-119 are canceled herein. Claims 114-116 and 130-138 are amended herein to specify that the fluorescence intensity of a population of cells is the mean fluorescence intensity. Support for this amendment can be found in the Description of Figure 11 (page 13, lines 6-17) where Applicants describe measurement of the mean fluorescent intensity for a population of hybridoma cells. Support can also be found in the Examples on page 74, lines 11-24 where Applicants provide further description of measuring mean fluorescence intensity. Therefore, Applicants believe that one of skill in the art would know what is meant by mean fluorescence intensity. Therefore, Applicants believe this rejection has been overcome and respectfully request its withdrawal.

Rejections Under 35 U.S.C. § 112, first paragraph

The Office Action states that claims 8-9 and 117-119 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was allegedly not described in

the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention.

Although Applicants believe that claims 8-9 and 117-119 are adequately enabled, in order to advance prosecution, claims 8-9 and 117-119 are canceled herein. However, Applicants preserve the right to pursue these claims in subsequent prosecution.

Rejections Under 35 U.S.C. § 102(b)

A. The Office Action states that claims 1-4 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Meilhoc et al. According to the Office Action, Meilhoc et al. teach a population of hybridoma cells wherein at least 90% of cells express a monoclonal antibody on the cell surface. Thus, the Office concludes that Meilhoc et al. anticipates claims 1-4.

Claim 1 is amended herein to recite “[a] population of hybridoma cells wherein greater than 15 % of the cells in the population express the endogenous membrane form of a monoclonal antibody that is bound to the cell surface and wherein the amount of monoclonal antibody bound to the cell surface is at least five fold greater than the amount of the endogenous membrane form of a monoclonal antibody bound to the cell surface of a population of hybridoma cells that does not comprise a vector comprising a nucleic acid encoding Igα and/or Igβ. Claims 2-4 are similarly amended.

Meilhoc et al. does not describe a population of hybridoma cells that exhibits an increase in the amount of the endogenous membrane form of a monoclonal antibody that is bound to the cell surface that is at least five fold greater than the amount of the endogenous membrane form of a monoclonal antibody bound to the cell surface of a population of control hybridoma cells that does not comprise a vector comprising a nucleic acid encoding Igα and/or Igβ. Therefore, Meilhoc et al. does not anticipate herein amended claims 1-4. Thus, Applicants believe this rejection has been overcome and respectfully request its withdrawal.

B. The Office Action states that claims 5-7, 10-13 and 16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Maciak et al.

Claims 5-7, 10-13 and 16 are canceled herein, thus rendering this rejection moot.

C. The Office Action states that claims 1-4 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Breitling et al. According to the Office Action, Breitling et al. teach a method of producing hybridoma cells which express monoclonal antibody molecules on the surface of the cell as detected by FACS analysis.

As stated above, claim 1 is amended herein to recite “[a] population of hybridoma cells wherein greater than 15 % of the cells in the population express the endogenous membrane form of a monoclonal antibody that is bound to the cell surface and wherein the amount of monoclonal antibody bound to the cell surface is at least five fold greater than the amount of the endogenous membrane form of a monoclonal antibody bound to the cell surface of a population of hybridoma cells that does not comprise a vector comprising a nucleic acid encoding Igα and/or Igβ. Claims 2-4 are similarly amended.

Breitling et al. do not disclose hybridoma cells that express increased amounts of the endogenous membrane form of a monoclonal antibody that is bound to the cell surface. Instead, Breitling et al. disclose the expression of the secreted form of a monoclonal antibody which is released into the culture medium and subsequently binds the hybridoma cell surface. Therefore, the secreted form of a monoclonal antibody described by Breitling et al., is not the endogenous membrane form of the monoclonal antibody that is expressed and presented on the cell surface of the hybridomas of the present invention. Therefore, Breitling et al. does not anticipate herein amended claims 1-4.

D. The Office Action states that claims 5-7, 10-13 and 16 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Maciak et al., Breitling et al.

As stated above, claims 5-7, 10-13 and 16 are canceled herein thus rendering this rejection moot.

#### Rejections Under 35 U.S.C. § 103(a)

A. Claims 1-7, 10-17, 19-22, 28-33, 42, 112-116, 120-121 and 130-138 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Matsuuchi et al. in view of Maciak et al. The Office Action states that Matsuuchi et al. teach a method of expressing membrane-associated antibody by co-expressing Igα and Igβ with the

antibody. According to the Office Action, co-expression of Ig $\alpha$  and Ig $\beta$  leads to an approximately 10-fold increase in the cell surface expression of the antibody as detected by fluorescence, such that approximately 75% of cells expressing Ig $\alpha$  and Ig $\beta$  have at least two-fold greater fluorescence intensity than cells not expressing these receptors and at least 10% of cells expressing Ig $\alpha$  and Ig $\beta$  have at least ten-fold greater fluorescence intensity than cells not expressing these receptors. Therefore, the Office concludes that the method taught by Matsuuchi et al. results in producing a cell comprising a vector, wherein the vector comprises nucleic acids encoding Ig $\alpha$  and Ig $\beta$ . The Office Action also states that Matsuuchi et al. does not teach a hybridoma cell comprising a vector, wherein the vector comprises nucleic acids encoding Ig $\alpha$  and Ig $\beta$ .

According to the Office Action, Maciak et al. teach the importance of obtaining maximal yields of antibodies from hybridoma cultures and that the yield is positively correlated with the surface expression of the antibody. Therefore, the Office Action states that one of ordinary skill in the art at the time the invention was made would have allegedly been motivated to do so, based on the teachings of Maciak et al. regarding the importance of obtaining maximal yields of antibodies from hybridoma cultures. Further stated in the Office Action is that the ordinary artisan would have had a reasonable expectation of success, based on the teachings of Matsuuchi et al. that surface-bound expression of antibody molecules can be achieved by co-expressing them with Ig $\alpha$  and Ig $\beta$  molecules.

As stated above, claims 5-7 and 10-16 are canceled herein. Applicants respectfully point out that although Maciak et al. teach that some hybridoma cells present a higher than average density of immunoglobulin on their cell surface, it is clear that Maciak et al. did not know how this immunoglobulin appeared on the cell surface nor did Maciak et al. know for certain that the immunoglobulin being detected on the hybridoma cell surface was the membrane form of the immunoglobulin. As stated in column 4, lines 59-68, “[h]ybridomas also have Mabs of the same type and specificity associated, either integrally or passively, with the outer surface of the plasma membrane. At present, the exact mechanism by which these Mabs appear on the cell surface is unknown and in any event, the present invention does not reside in such mechanism.” Therefore, since Maciak et al. did not know the mechanism by which some monoclonal antibodies become

associated with the membrane, Maciak et al. also did not disclose or suggest that the amount of the membrane form of a monoclonal antibody on the cell surface of a hybridoma cell could be increased by any means.

It is the present invention that not only shows that the endogenous membrane form of a monoclonal antibody can be increased on the cell surface of a hybridoma cell, but also provides, for the first time, hybridoma cells where this consistently occurs and methods of making these hybridomas. It is clear that Maciak et al. were relegated to making the most of a naturally occurring phenomenon that allows isolation of randomly occurring hybridoma cells with above average density of monoclonal antibody on the hybridoma cell surface. Although this might translate as a wish that more hybridomas had this level of expression, this is not equivalent to solving the problem that applicants have solved which is consistently providing hybridoma cells with at least a two fold increase in the amount of the endogenous membrane form of the monoclonal antibody bound to the cell surface.

Even if one of skill in the art were motivated by Maciak et al. to increase the amount of monoclonal antibody on a hybridoma's cell surface, Matsuuchi et al. does not disclose or suggest any hybridoma, much less any hybridoma with increased amounts of the endogenous membrane form of a monoclonal antibody bound to the cell surface or any method of consistently producing a hybridoma with at least a two fold increase in the amount of the endogenous membrane form of a monoclonal antibody bound to the cell surface.

Furthermore, there is no indication in Matsuuchi et al. that the results obtained by transfecting a nucleic acid encoding Ig $\alpha$ , a nucleic acid encoding Ig $\beta$  and a nucleic acid encoding the membrane form of the  $\mu$  heavy chain into AtT20 pituitary cells would result in an increase in the amount of monoclonal antibody bound to the surface of any other type of cell, much less a hybridoma cell. In fact, on page 3405, col. 2, Matsuuchi et al. states that "...MB-1 and Ig $\beta$  were sufficient for surface expression of mIgM in nonlymphoid cells." (Emphasis added) Matsuuchi et al. further emphasizes this on page 3407 where it is stated that "[o]ur results demonstrate that MB-1 and Ig- $\beta$  are the only B cell specific components required for cell surface expression of mIgM in a nonlymphoid cell line." (Emphasis added) Therefore, the Matsuuchi et al. reference says nothing about



the requirements for cell surface expression of mIgM in a hybridoma cell, which is derived from a lymphoid line. Thus, it cannot be assumed that the results obtained in one cell will be equivalent to results obtained in another cell, particularly if the cells are of different lineages.

Furthermore, Matsuuchi et al. transfected a nonhybridoma cell with the nucleic acids encoding Ig $\alpha$  and Ig $\beta$  as well as a nucleic acid encoding the membrane form of the  $\mu$  heavy chain. The increases observed by Matsuuchi et al. in a nonhybridoma cell that does not produce antibodies cannot be interpreted as equivalent to increases, if any, that one of skill in the art would see in an antibody producing cell, such as a hybridoma cell, which is predisposed to secrete massive amounts of monoclonal antibody and, as will be discussed below, does not favor the production or presentation of the membrane form of a monoclonal antibody. Furthermore, since the experiments were performed in a non-antibody producing cell, with an artificially introduced membrane form of the  $\mu$  heavy chain, the increases seen by Matsuuchi et al. pertain to increases in a recombinant form of the  $\mu$  heavy chain and not to increases in the endogenous membrane form of a monoclonal antibody. Matsuuchi et al.'s results in no way disclose or suggest that the endogenous membrane form of a monoclonal antibody normally produced by a hybridoma cell (i.e., the membrane form of the monoclonal antibody with the specificity acquired from the B cell utilized to make the hybridoma cell) can be consistently presented on the membranes of hybridoma at levels that allow efficient labeling and selection of hybridoma cells. Also, by conducting experiments in nonhybridoma cells, there was no need for Matsuuchi et al. to overcome the predisposition of an antibody producing cell to secrete antibodies instead of presenting them on their membranes.

Applicants overcame the hybridoma cell's predisposition to secrete monoclonal antibodies instead of presenting the membrane form of the monoclonal antibodies on their cell surface. Therefore, the hybridoma cells of the present invention consistently express increased amounts of the endogenous membrane form of monoclonal antibodies on their cell surface while maintaining their secretory abilities, thus solving a long existing problem in the art. By consistently increasing the endogenous membrane form of the monoclonal antibodies on the cell surface of hybridoma cells, one of skill in the art can efficiently label and sort cells that produce a desired antibody, thus replacing current,

tedious antibody screening and limit dilution procedures, with a rapid, high throughput selection process.

In further support of the nonobviousness of the present invention, Applicants point out that it is well known in the art that hybridoma cells are the result of fusion between tetraploid myeloma cells with diploid lymphocytes or B cells. As a result, genetic instability is associated with hybridoma cells. Therefore, there was no reasonable expectation that the transfection and expression results obtained in an AtT20 cell (endocrine cell utilized by Matsuuchi et al.) would be reproducible in any other cell, much less in a cell of different lineage, i.e. a hybridoma cell, with unpredictable genetic composition. Therefore, until the present invention, one of skill in the art could not reasonably expect that transfection of nucleic acids encoding cell surface receptors Ig $\alpha$  and/or Ig $\beta$  into hybridoma cells or a myeloma fusion partner would result in any expression of the receptors on the cell surface of a hybridoma, much less the pattern and level of expression seen in a hybridoma cell such that an increase in the amount of the endogenous membrane form of a monoclonal antibody bound to the cell surface of the hybridoma occurs.

In fact, it was known in the art that myeloma cells, which are malignant plasma cells derived from B cells, do not express the Ig $\alpha$  receptor despite the fact that this receptor is expressed in early and normal B cells, (Sakaguchi et al. "B lymphocyte lineage-restricted expression of mb-1, a gene with CD3-like structural properties" EMBO 7(11) p.3457-3464)(copy attached) from which a myeloma cell is derived. Therefore, as B cells differentiate into plasma cells, the gene for the Ig $\alpha$  receptor is downregulated. Since transcription of this gene is silenced in myeloma cells, at the time of the present invention, one of skill in the art had no reasonable expectation that transfection of a nucleic acid encoding Ig $\alpha$  into a myeloma cell which does not express this gene, would result in expression of Ig $\alpha$ , that could be sustained in a hybridoma cell produced by fusing the transfected myeloma cell with B cells. Furthermore, since hybridoma cells are derived from myeloma parent cells that are predisposed to not express Ig $\alpha$ , and myeloma cells often impart their phenotype to the resultant hybridoma cell, one of skill in the art would not have had a reasonable expectation of success that transfection of hybridoma cells with a vector comprising a nucleic acid encoding Ig $\alpha$  and/or Ig $\beta$  would result in any

expression of these receptors and ultimately in increased amounts of the endogenous membrane form of the monoclonal antibody bound to the cell surface of hybridoma cells. Nothing in the art would indicate that one of skill in the art could reasonably expect that the hybridoma cell could overcome the myeloma partner's predisposition to silence Ig $\alpha$  and express Ig $\alpha$  to any appreciable extent.

As stated above, a hybridoma is derived from a myeloma parent cell and a lymphocyte cell. The myeloma cell partner confers the ability to grow indefinitely in culture while the genetic information which codes for antibody specificity and type emanates from the lymphocyte. In addition to imparting the ability to grow indefinitely, upon fusion with a lymphocyte, a myeloma cell also markedly increases the tendency of hybridoma cells to favor production and secretion of the secretory form of monoclonal antibodies. Milcarek et al. ("Changes in Abundance of IgG 2a mRNA in the Nucleus and Cytoplasm of a Murine B-Lymphoma Before and After Fusion to a Myeloma Cell" *Mol. Immunol.* 33: 691-701 (1996) (copy attached) showed that after fusion of myeloma cells with a memory B cell line, production of the secretory specific form of Ig heavy chain mRNA predominated over that of the membrane encoding form by 100:1. Milcarek et al. attribute this 100 fold increase in the ratio of secretory versus membrane forms of the immunoglobulin heavy chain in the hybrids to a 10 fold decrease in the production of the membrane form of the immunoglobulin by post-transcriptional RNA processing events whereas the overall amounts of nuclear RNA remain relatively constant between the hybrid cells and the B cells (see page 698, col. 2, last paragraph). Also contributing to the myeloma-like phenotype of the hybrid cells is a decrease in the nuclear to cytoplasmic ratio for the secretory form of the  $\gamma$ 2a immunoglobulin in the hybrid cells compared with the parent lymphoid cell line, with a smaller apparent change in the nuclear to cytoplasmic ratio for the  $\gamma$ 2a membrane encoding form (see page 699, col. 2). Milcarek et al. also note that the numbers obtained for the membrane encoding form are small and therefore difficult to quantitate accurately.

Based on Milcarek's results, it is evident that the membrane form of the immunoglobulin is produced in small quantities in a lymphoid cell (e.g. a B cell) and that once fusion occurs with a myeloma cell, the amount of the membrane form of the immunoglobulin is further reduced by post-transcriptional processing events.

Furthermore, the amount of the membrane form produced is overwhelmed by production of the secretory form of the antibody, such that the hybridoma heavily favors the myeloma phenotype and thus secretion of the monoclonal antibody. Therefore, a method of increasing the amount of the membrane form of the immunoglobulin on the cell surface of the hybridoma and the hybridoma cells produced by these methods would not have been obvious because all indications pointed to decreases in the production of the membrane form of the immunoglobulin. Given the fact that fusions of B cells with myeloma cells result in decreased amounts of the membrane form of the immunoglobulin and a significant increase in the secretory form of the immunoglobulin, one of skill in the art could not expect that the endogenous membrane form of the immunoglobulin was produced to any appreciable extent, much less that it could be presented via any method at consistently detectable levels in hybridoma cells.

It was not until the present invention that this was possible, thus solving an intractable problem in the art of hybridoma labeling and selection. Not only did Applicants show that the Ig $\alpha$  and Ig $\beta$  receptors could be adequately expressed on the cell surface of hybridoma cells, but Applicants provided the unexpected discovery that the endogenous membrane form of the monoclonal antibody normally produced by the hybridoma cell is moved into the cell membrane of hybridoma cells in the presence of the Ig receptors to significantly increase the amount of monoclonal antibody bound to the cell surface of hybridoma cells. Given the unpredictability of cell fusions and data (Milcarek et al. 1996) showing that hybridoma cells favor decreased expression and decreased presentation of the endogenous membrane form of immunoglobulins, the hybridoma cells of the present invention that reliably express increased levels of the endogenous membrane form of the immunoglobulin represent a significant breakthrough in the field of monoclonal antibody technology. Therefore, it would not have been obvious for one of skill in the art to combine Maciak et al. with Matsuuchi et al. to arrive at the hybridomas of the present invention. Therefore, Applicants believe that this rejection as it pertains to claims 1-4, 17, 19-22, 28-33, 42, 112-116, 120-121 and 130-138 has been overcome. Thus, Applicants respectfully request its withdrawal.

B. Claim 34 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Matsuuchi et al. in view of Maciak et al. and further in view of Gossen et al.

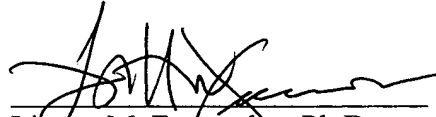
For the reasons discussed above, one of skill in the art would not have combined the teachings of Matsuuchi et al. with the teachings of Maciak et al. to arrive at the claimed invention. Therefore, it would not have been obvious to combine the teachings of Matsuuchi et al. with the teachings of Maciak et al. with the teachings of Gossen et al., directed to the use of inducible promoters to arrive at the claimed invention. Therefore, applicants believe this rejection has been overcome and respectfully request its withdrawal.

In view of the above remarks, reconsideration and allowance of the pending claims is believed to be warranted and such action is respectfully requested. The Examiner is encouraged to directly contact the undersigned if this might facilitate the prosecution of this application to issuance.

A Credit Card Payment Form PTO-2038 authorization payment in the amount of \$660.00 and a Request for Extension of Time are included herewith. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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**CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8**

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

  
Lizette M. Fernandez

Date 9/6/05

**Amendments to the Drawings**

Attached hereto is a replacement sheet for Figure 13. Please replace the drawing sheet with Figure 13 with this replacement drawing sheet.